GASTROINTESTINAL DRUGS ADVISORY COMMITTEE BACKGROUND PACKAGE

GI Drugs Advisory Committee November 16th, 2011	Discussion of Trial Designs to Establish Safety and Efficacy of Repeated Dosing Cycles of Rifaximin for "Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D) in patients greater than 18 years of age".
Division	Division of Gastroenterology and Inborn Errors Products
Established Name	Rifaximin
Trade Name	Xifaxan®
Therapeutic Class	Miscellaneous class semi-synthetic antibiotic derived from rifamycin
Applicant	Salix Pharmaceuticals, Inc.
Formulation(s)	Immediate release tablet
Proposed Dosing Regimen	550mg orally three times per day for 14 days
Indication(s)	Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D), in patients ≥18 years of age
Intended Population(s)	Patients 18 years of age and older with Irritable Bowel Syndrome with Diarrhea

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the issue of the design of retreatment trials for rifaximin for treatment of Irritable Bowel Syndrome with Diarrhea to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Executive Summary

On March 8, 2011 Salix Pharmaceuticals, the manufacturer of Xifaxan (rifaximin), announced in a press release that the company received a "Complete Response Letter *(CRL)* on March 7, 2011 for the supplemental New Drug Application (sNDA) for XIFAXAN® (rifaximin) 550 mg tablets for the proposed indication of treatment of non-constipation irritable bowel syndrome (Non-e IBS) and IBS-related bloating" from the FDA. The release stated that the reason for this is "due to a newly expressed need for retreatment information."

There are no antibiotics approved for the treatment of IBS. Antibiotics have been used off label for the treatment of IBS, and are even mentioned in the American College of Gastroenterology (ACG) guidelines for management of irritable bowel syndrome. The ACG guideline for treatment of IBS states, "A short-term course of a nonabsorbable antibiotic is more effective than placebo for global improvement of IBS and for bloating (rated as weak evidence with a moderate recommendation level).[1] There are no data available to support the long-term safety and effectiveness of nonabsorbable antibiotics for the management of IBS symptoms." The current FDA approved drugs for IBS treatment have much different mechanisms of action and were administered continuously during the treatment periods of the trials conducted to support their approval (usually 12 weeks). The proposed mechanism of action and dosing paradigm for rifaximin (Xifaxan®) presented unique challenges in evaluation of this application.

The proposal that small intestinal bacterial overgrowth (SIBO) was the underlying cause of IBS in the patients enrolled in the trials conducted to support rifaximin's New Drug Application (NDA) was not proven as part of the clinical trial conduct. Others in the academic community have recently concluded that the bacterial theory of IBS is not yet fully developed, that the data are incomplete so far, and that the theory does not yet meet the basic epidemiological criteria of causality.[2,3,4] In a recent double-blind placebo controlled antibiotic study in SIBO that enrolled children with chronic abdominal pain, rifaximin was not found to be effective, in improving symptoms, despite improvement in the lactulose breath testing[5].

Salix performed two large, randomized, placebo-controlled pivotal trials in support of the supplemental NDA for the IBS indication. The trials enrolled only patients with IBS with diarrhea and also excluded patients with severe symptoms. The primary endpoint was global improvement in symptoms of IBS and the secondary endpoint was global improvement in bloating. Rifaximin (Xifaxan®) was dosed for only two weeks, and then efficacy was evaluated for the four weeks following the two week treatment period. Overall response was defined as response for at least 2 of the 4 weeks of the primary efficacy period (PEP), weeks 3 thru 6. The patients were monitored for 6 additional weeks. The results of both trials showed a response rate difference from placebo of 9 to

11% for the specified primary and secondary endpoints (during weeks 3 thru 6). There was a high placebo response rate, as has been commonly seen in IBS trials.

The applicant presented data that they proposed demonstrated that response was sustained for the entire 12 weeks of the trial. The FDA analyses of the efficacy data observed a loss of efficacy at weeks 6 or 7 in each trial for both end-points and in the subgroup that responded during the Primary Efficacy Period (weeks 3 thru 6). Additionally it was noted that the difference in the treatment effect between the rifaximin and control group was only 9 to 11%.

There were review concerns raised regarding the potential for development of antibiotic resistance, which could not be mitigated, given the lack of data on changes in bacterial flora or susceptibility in the setting of long term or repeated use of rifaximin. Repeated courses of any antibacterial drug in a population will eventually result in some degree of increase in minimum inhibitory concentrations (MICs) of the antibacterial and in clinical failures. If an antibiotic provides marginal clinical improvement, then the potential risk of development of resistance and cross-resistance with other similar drugs (e.g. rifampin) in other bacteria takes on greater weight in the risk/benefit analysis. In fact there have been recent reports of clinical *C. difficile* isolates with high-level resistance to rifaximin. In addition, organisms with high rifaximin MIC values also have elevated MIC values against rifampin. However, the clinical relevance of such findings remains unknown.[6,7]

The current FDA precedent for an antibiotic treatment for chronic intermittent use in cystic fibrosis-related Pseudomonas aeruginosa infection, which is life threatening, mandates a stronger clinical trial development program than that submitted for rifaximin. TOBI® is administered in repeated cycles of 28 days on drug followed by 28 days off drug. It was studied in two identically designed, double-blind, randomized, placebo-controlled, parallel group, 24-week clinical studies for three cycles of administration.

In conclusion, although the applicant did provide evidence of the short term efficacy of rifaximin in patients with mild to moderate IBS-D, the FDA determined that it is important for patients with chronic conditions to have information about how and when a product should be administered beyond the first cycle of therapy. In addition, patients and their health care providers should have information on the safety and effectiveness of retreatment. Intermittent treatment is a unique treatment paradigm in drug development programs for treatment of IBS. The Division and Salix have elected to convene this Gastrointestinal Drugs Advisory Committee to discuss the issues raised in the review and to ask the Committee to assist in development of appropriate future trial designs to establish the safe and effective, long term administration schedule of rifaximin in IBS-D.

1 Introduction to Advisory Committee Meeting

The Division of Gastroenterology and Inborn Errors Products (DGIEP) received a New Drug Application (NDA) from Salix Pharmaceuticals to add a new indication and dosing regimen for rifaximin for the treatment of non-Constipation Irritable Bowel Syndrome (non-C IBS) on June 7th 2010. In the NDA supplement, Salix proposed to market rifaximin 550 mg immediate release tablet capsule for the following indication:

> Treatment of Non-constipation Irritable Bowel Syndrome (IBS), and IBS related bloating in patient's ≥18 years of age

The Division issued a Complete Response letter to Salix citing the reasons for its decision not to allow marketing of rifaximin for IBS treatment at this time. The major concerns raised by the review division were:

1. The documented duration of treatment effect (approximately 4 weeks) was inadequate for a chronic condition, in light of the absence of data on efficacy of repeat courses of treatment.

2. The FDA reviewers did not agree that the statistical analysis supported a conclusion that the treatment effect was durable over the 12 weeks of the trial. (See more detailed discussion under Section 8.5 on page 33 and Section 9.5 on page 41).

3. The applicant failed to identify the patient population most likely to benefit from antibiotic treatment, and did not study patients that would be treated if the proposed indication had been approved.
   a. The applicant theorizes that non-C IBS patients with Small Intestinal Bacterial Overgrowth (SIBO) would be responders, but SIBO was not an eligibility criterion in the clinical trials. Neither bacterial cultures nor other biomarker testing was performed during the trials to attempt to establish proof of the proposed mechanism.
   b. The application did not support an indication for a non-C IBS population, as only IBS-D patients were included in the trials.
   c. The trials excluded patients with severe symptoms. It is important to characterize whether the product will be effective in patients with severe symptoms.

4. In light of the anticipated repeated use of rifaximin in a large proportion of the US population with non-constipation IBS, concerns were raised about the development of resistant bacteria and the potential for serious enteric infections. Concerns were raised about the use of an antibiotic without

establishment of an underlying infection and the possible public health consequences that this may pose in the future.

Members of the FDA review team expressed concern that the applicant had not adequately justified the rifaximin dose and length of treatment that were selected for study in the randomized, controlled efficacy trials submitted in support of the NDA. While this was not considered a reason for the complete response action for this product, it was noted in the clinical pharmacology review. See discussion under Section 5.

The European Medical Societies' (EMA) "Points to Consider on the Evaluation of Medicinal Products for the Treatment of Irritable Bowel Syndrome (IBS)" supports the FDA reviewer's concerns regarding the limitations posed by the single treatment cycle rifaximin trials submitted in support of the IBS indication. Importantly the document states "demonstration of efficacy with repeated use would also be required for a short term indication and a minimum of two cycles would be needed" as the use of the medication will be used chronically." The failure to demonstrate the durability of response of a single treatment of a disease that is characterized by chronicity and intermittency of signs and symptoms is important. The lack of durability of response of rifaximin and the lack of demonstrating efficacy of a retreatment regimen is not sufficient proof of efficacy in a chronic disease such as IBS.

The Division and Salix have elected to convene this Gastrointestinal Drugs Advisory Committee to seek the assistance of the Committee in development of trial designs to address the issues raised in the FDA's review of this proposed new indication for rifaximin, with the goal of obtaining adequate information for product labeling to guide patients and their health care providers on how to safely and most effectively administer rifaximin in IBS. . The questions below should be considered in developing future trial designs to address the knowledge gaps identified during the initial review. A study design for consideration is presented in Section 2 Design of Trials to Evaluate Efficacy and Safety of Retreatment Cycles in IBS of this briefing document.

- What should be the major goal of rifaximin retreatment for IBS?
  - Prevention of recurrent symptoms (starting treatment before symptoms occur or utilizing a "maintenance regimen" of chronic dosing)
  - Treatment of recurrent symptoms (starting treatment when symptoms return)
  - Induction of 'cure' or 'long term remission'

- What trial design will best define the appropriate dosing interval for future product labeling for each goal listed above?

- Should other dose levels and durations of treatment be explored?

- How should the correct population for this treatment be identified? Is there a role for a biomarker in the proposed trials to enrich the population? If so, which one(s), for what purpose, and in what order of priority?

- What other efficacy information needs to be acquired to support adequate labeling? What other safety information needs to be acquired to support adequate labeling? Which information needs to be acquired premarketing?

- How should development of antibiotic resistance to rifaximin be monitored?

2 Design of Trials to Evaluate Efficacy and Safety of Retreatment Cycles in IBS

IBS has been a very difficult disease syndrome in which to conduct clinical trials due to the high placebo response rate (often as high as 30-40%), and the intermittency of symptoms and signs. The signs and symptoms of IBS are also a common response to a diverse group of pathologies. A clinical trial design that targets patients who are more likely to respond to therapy may produce better and more interpretable efficacy results.

During the time leading up to this Advisory Committee meeting, FDA and Salix have worked together to develop a trial design proposal to address questions regarding efficacy of repeat rifaximin dosing in IBS (See Figure 1). The design would involve an initial screening period followed by treatment with rifaximin for two weeks. There would be a two to four week efficacy evaluation period followed by a variable period off treatment with re-randomization to placebo or rifaximin when symptoms recur. The data from a minimum of two treatment cycles would be required to be submitted to the FDA for consideration of marketing approval. Salix has proposed that efficacy data from the third cycle would be submitted post marketing. By selecting responders or partial responders with the first cycle of rifaximin, the population will be enriched by removing non-responders; however this may be confounded by the high placebo response rate in IBS trials.

Proposed Retreatment Trial Design:
This is a multi-center, randomized, double-blind, placebo-controlled, phase-3 trial in subjects with non-Constipation Irritable Bowel Syndrome (non-C IBS). Subjects will receive rifaximin for the initial treatment for 2 weeks with a 2-week treatment-free follow-up. Subjects who achieve treatment success in both IBS-related abdominal pain AND stool consistency for at least two of the first four weeks in the study will be classified as responders and enter a treatment free Maintenance Phase 1. Non-responders will be withdrawn from the study. The treatment free Maintenance Phase 1 is variable in duration (up to 20 weeks in total) and depends upon time each patient experiences symptom recurrence (defined as absence of treatment success in both IBS-related abdominal pain AND stool consistency).

The Primary objective is to evaluate the efficacy of repeat treatment with rifaximin 550mg TID (2 weeks treatment; 2-week treatment-free follow-up) in subjects with IBS-D who responded to initial treatment with rifaximin 550 mg TID (2 weeks treatment; 2-week treatment-free follow-up).

Subjects with recurrence will enter the Double-Blind, Randomized Treatment (DBR) Phase. In the DBR Phase subjects will be randomized 1:1 to receive either rifaximin 550 mg TID or placebo TID for 2 weeks with a 2-week treatment-free follow-up, then enter a second treatment free phase for up to 8 weeks (Maintenance Phase 2). All subjects from Maintenance Phase 2 who meet criteria for recurrence will enter a Second Repeat treatment Phase (SRT) where they will receive the same treatment as per previous randomization (rifaximin 550 mg TID or placebo TID for 2 weeks with a 2-week treatment-free follow-up).

The study will consist of the following Phases:

- Screening Phase (up to 30 days)
  Potential subjects will be required to undergo screening assessments including colonoscopy (if necessary) and to complete the Diary Eligibility Period. The Diary Eligibility Period will begin no earlier than 7 days after the colonoscopy procedure and within 10 ± 3 days prior to the Randomization Visit. If no colonoscopy is required, the diary eligibility visit may be combined with the Screening Visit. During the Diary Eligibility Period, subjects will be required to respond to daily IBS symptom related questions for at least 7 days. The Screening Phase will last no longer than 30 days. Eligible subjects will enter the Initial Treatment Phase.

- Initial Treatment Phase: (Day 1)
  All subjects will receive rifaximin 550 mg TID for 2 weeks with a 2-week treatment-free follow-up. At Week 4, subjects will be assessed for response to treatment. Responders will continue into Maintenance Phase 1, non-responders will withdraw from the study.

- Maintenance Phase 1 (Visit 5)
  Subjects eligible for Maintenance Phase 1 will continue with an additional treatment-free follow-up period.
    - Subjects will continue making diary calls and will be continually assessed for ongoing response as well as recurrence based on the previous 4 weeks starting at the end of the second week of Maintenance Phase 1 and the end of each week thereafter, such that each week begins a new consecutive 4-week assessment period. Subjects who meet criteria for recurrence will enter the DBR Phase.
    - Subjects who do not meet recurrence criteria by the end of the 8th week of Maintenance Phase 1 will be allowed to continue for up to an additional 12

weeks until they either experience recurrence; or until enrollment is met in the DBR Phase.

- DBR (First Repeat) Treatment Phase Visit 6
    - Subjects who meet criteria for recurrence will be re-randomized 1:1 to receive:
        a. Rifaximin 550 mg TID for 2 weeks with a 2-week treatment-free follow-up OR
        b. Placebo TID for 2 weeks with a 2-week treatment-free follow-up

- Maintenance Phase 2
  All subjects meeting criteria for responder at the end of the DBR Phase will be eligible for Maintenance Phase 2 and will continue with an additional treatment-free follow-up period of up to 8 weeks.
    - Subjects will continue making diary calls and will be continually assessed for ongoing response as well as recurrence based on the previous 4 weeks starting at the end of the second week of Maintenance Phase 2 and the end of each week thereafter, such that each week begins a new consecutive 4-week assessment period. Subjects who meet criteria for recurrence will enter the Second Retreatment (SRT) Phase.
    - Subjects who do not meet recurrence criteria by the end of the 8 week Maintenance Phase 2 will be withdrawn.
- Second Retreatment Phase (SRT-Day 1)
    - For the SRT, subjects will receive the same treatment per randomization as in DBR Phase:
        a. Rifaximin 550 mg TID for 2 weeks with a 2-week treatment-free follow-up OR
        b. Placebo TID for 2 weeks with a 2-week treatment-free follow-up

The total study duration (including the Screening Phase) is approximately 32 weeks, depending on time of recurrence of disease and whether a colonoscopy is required. Primary efficacy analysis will be performed at the end of the DBR Phase (approximately 16 weeks after the start of the Initial Treatment Phase).

Reviewer's Comment:
The sponsor proposed study design evaluates administration of repeat rifaximin cycles that are started only after patients become symptomatic again, specifically those patients who become symptomatic again 12 -16 weeks after having started their previous cycle of rifaximin.

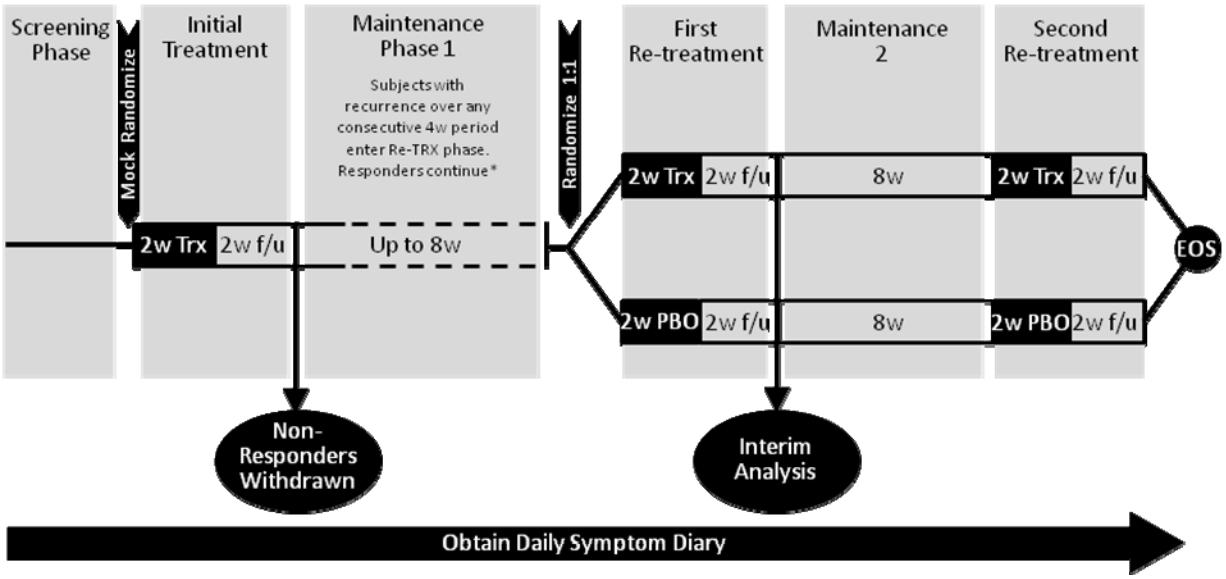
This design does not include a placebo arm in initial treatment period and maintenance phase 1. An advantage of having placebo arm in initial treatment period and maintenance phase 1 is that results from initial treatment period and maintenance phase 1 can be used to evaluate whether results from previous studies (RFIB3007 and

RFIB3008) could be replicated. Additionally, because the new trial will be based on the current FDA Draft Guidelines for IBS (which has different entry criteria than was used in the previous rifaximin trials) there may be some differences in the population. However, inclusion of a placebo arm at these points of the trial would require a very large trial population and may not be practical.

The rolling 4 week assessment of recurrence may be difficult to interpret. The first three weeks will drive the outcome of the assessment, such that if a patient is a responder for the at least two of first 3 weeks, but not on the last week, they will still be considered a responder (no recurrence). For this reason, it seems that recurrence assessment would most appropriately be performed every two weeks or every four weeks.

This design assumes that the dose initially selected for study is the optimal dose and that the 14 day treatment cycle duration is also optimal.

Figure 1: Study Design Schematic



*Subjects who do not meet disease recurrence criteria by the end of the Maintenance Phase 1 will be allowed to continue up to 24 weeks in total from mock randomization until they experience disease recurrence; or until enrollment is met in the FRT Phase.

The Division would like the applicant to consider investigating the use of breath testing as a potential diagnostic marker of SIBO during this trial. Recent literature has suggested that combining breath testing with scintigraphy could distinguish rapid transit from SIBO, yielding higher specificity than current diagnostic criteria using signs and symptoms allow.[8,9,10] Study design elements, including standardized breath testing,

that have the potential for identifying patient characteristics associated with being a responder, should be incorporated in this trial.

The study design will be fully presented by Salix and FDA at the course of the Advisory Committee meeting.

3 Background Information

3.1 Introduction

Rifaximin is a nonaminoglycoside, semisynthetic antibiotic derived from rifamycin. Rifaximin has antimicrobial activity of varying levels against Gram-positive, Gram-negative, aerobic, and anaerobic enteric bacteria similar to its parent compound. Rifaximin acts primarily by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase, resulting in inhibition of bacterial RNA synthesis.

The proposed indication is for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in patient's ≥ 18 years of age. The proposed dose of rifaximin is 550 mg taken orally 3 times a day, for 14 days.

Rifaximin was initially approved in 2004 for the treatment of Traveler's Diarrhea at a dose of 200mg b.i.d for 3 days in patient's ≥12 years of age. It was subsequently approved in 2010 for reduction in risk of overt Hepatic Encephalopathy (HE) episodes, at a dose of 550mg b.i.d., continuously, in patient's ≥18 year of age.

3.2 Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by debilitating and recurring abdominal pain, bloating, and altered bowel function (constipation, diarrhea, or alternating diarrhea and constipation) in the absence of any organic cause. The prevalence of symptoms of IBS in North America appears to be 10% to 15% of the general population.[11] IBS is one of the leading reasons for consultation with a primary care physician. The symptoms of IBS cause substantial impairment in health-related quality of life and lead to increased health resource utilization and reduced work productivity. Despite the pervasiveness, incapacitating symptoms, and medical costs associated with IBS, treatment options remain limited.

There are four currently recognized subtypes of IBS; Irritable Bowel Syndrome with diarrhea, IBS with constipation, mixed or alternating IBS and un-subtyped IBS. To these sub-types some investigators add bloating-predominate IBS, and pain-predominate IBS. The applicant enrolled only patients with IBS with diarrhea (IBS-D) in their randomized, controlled phase 3 trials.

The diagnosis of IBS is based on clinical symptoms, and there has been a gradual evolution of the diagnostic criteria. The applicant used the ROME II criteria in the clinical trials; however ROME III criteria are the current standard. The ROME II criteria define the syndrome as follows:

At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features:

1. Relieved with defecation and/or
2. Onset associated with a change in frequency of stool; and/or
3. Onset associated with a change in form (appearance) of stool

The pathophysiology of IBS is not well understood but is thought to be multifactorial. Currently it is thought that patients may have predisposing genetic or environmental factors and that precipitating factors may include such things as acute gastroenteritis. Patients then develop gastrointestinal motor disturbances, followed by visceral hypersensitivity, and abnormal central processing of symptoms. Food and emotional stress may play a role in the waxing and waning of symptoms frequently seen in this syndrome.

The American College of Gastroenterology has published treatment guidelines for IBS. These guidelines include:

- Psyllium hydrophilic mucilloid PEG laxatives
- Antispasmodic Agents/Peppermint oil
- Antidiarrheals/loperamide
- Antibiotics/rifaximin (the guidelines note the absence of long-term data)
- Probiotics/*Bifidobacteria*
- $5HT_3$ receptor antagonists/alosetron
- $5HT_4$ (serotonin) receptor agonists/ tegaserod
- Selective C-2 chloride channel activators/ lubiprostone
- Antidepressant agents/Tricyclic antidepressants (TCA) and Selective Serotonin Reuptake Inhibitors (SSRI)
- Psychological therapy - cognitive, dynamic psychotherapy, hypnotherapy
- Herbal therapy and Acupuncture (the guidelines note data are inconclusive)

3.3 Small Intestinal Bacterial Overgrowth (SIBO) and IBS

There are multiple ongoing hypotheses attempting to explain the pathophysiology of IBS. One hypothesis suggests that altered intestinal microbiota secondary to Small Intestinal Bacterial Overgrowth (SIBO) may be the cause of IBS symptoms in some patients. However, the definition of, and correlation of SIBO with IBS has not been established. There are experts who strongly believe that SIBO is under diagnosed; and others who state that there is inadequate proof that there is a correlation between the

two. The increase in bacterial counts in the upper small intestine noted in some IBS studies may be the result of the underlying dysmotility, and under those circumstances SIBO will recur until the dysmotility is corrected.

3.4 Biomarkers for Small Intestinal Bacterial Overgrowth (SIBO)

There are currently no validated tests to determine if patients with IBS have SIBO. Testing with endoscopy and culture has yielded an incidence of SIBO as low as 4%. Hydrogen breath testing using lactulose as the test substance, which has poor sensitivity and specificity, has yielded positive results varying between 20 and 80%. The definition of $>10^5$ cfu/ml in bacterial cultures collected from the small intestine has been used as a "gold standard" for diagnosis of SIBO. However, this definition was established in patients with altered GI anatomy from surgical procedures, e.g. a blind loop syndrome from a Billroth II surgical procedure. The definition of SIBO in patients diagnosed with IBS may be different. Literature review suggests that cultures from the small bowel at the Ligament of Treitz generally yield 10-100 CFU/ml in healthy individuals. The incidence of patients with cultures higher than 100 CFU/ml in patients with IBS has variously been reported to be between 38 and 84%. If SIBO truly is a significant pathological condition in IBS it would most likely be associated with culture results of $<10^5$ CFU/ml, and would have entirely different diagnostic criteria from those established in surgical patients ($>10^5$ CFU/ml).

There is extensive literature on the use of breath testing to diagnose SIBO; however, the accuracy of this type of testing has not been firmly established and the validity of the test remains in question. The most commonly used breath test for SIBO is the Hydrogen Breath Test after lactulose ingestion. Hydrogen breath tests are based on the fact that there is no source for hydrogen gas in humans other than bacterial metabolism of carbohydrates in the GI tract.

The diagnostic pattern of early hydrogen production by bacteria in the small intestine before the lactulose enters the colon can be confounded by rapid transit time thru the small intestine with early entry into the colon. The amount of time hydrogen levels should be measured is also not standardized. Cut off values for the level of hydrogen considered to be significant are different in different trials, and are not universally established. The elimination of the hydrogen produced by bacterial fermentation depends significantly on methanogenic and sulfate-reducing bacteria that convert hydrogen to methane and hydrogen sulfide. These organisms are highly competitive so that the stool of an individual contains high concentrations of only 1 of these 2 types of organisms. Therefore some individuals may be hydrogen negative secondary to metabolism of hydrogen by high levels of methane-producing bacteria.

There is clearly a need for new validated tests for IBS in order to facilitate research, to advance therapies and to improve patient diagnosis. Validation of a new diagnostic test requires data demonstrating, at a minimum, the concordance of the test results with clinical truth standard (or gold standard, when one is available) for that condition in the population of people in whom the test would be considered. If SIBO is the underlying etiology of IBS in at least a subpopulation of patients with IBS, the complexity for validating a new diagnostic test to identify this subpopulation rests in establishing a gold standard for SIBO in IBS patients. As referred to earlier, recent literature has suggested that combining breath testing with scintigraphy could yield higher specificity than current diagnostic criteria of signs and symptoms. A properly designed study allows the estimation of a test's predictive value, sensitivity, and specificity. The discovery and validation of new biomarker tests in this area has been challenging, in part because of the variability of the patient population and disease presentation, and the lack of clear diagnostic gold standards.

4 Nonclinical and Clinical - Toxicology/Pharmacology/Microbiology

4.1 Nonclinical Pharmacology/Toxicology

The sponsor did not conduct any new nonclinical studies for this application; they referenced the previous nonclinical studies conducted to support the prior two approved indications. There were no new nonclinical issues.

Reviewer's Comment:
It should be noted that the nonclinical studies submitted by the applicant with the NDA supplement for Hepatic Encephalopathy (HE), were limited in their ability to provide meaningful information about the potential systemic toxicity of rifaximin, as all the studies were done in healthy animals where the absorption of orally administered rifaximin was minimal. The applicant has a pending Post Marketing Requirement from the NDA for rifaximin for Hepatic Encephalopathy to study the effects of the drug in animals at increased systemic exposures.

4.2 Clinical Pharmacology

In support of the proposed indication, the sponsor provided single dose and multiple dose pharmacokinetics data in patients with non-constipation IBS and a drug interaction study between rifaximin and oral contraceptive. In addition, in vitro studies to identify metabolizing enzymes, effects of rifaximin on the inhibition and induction of cytochrome P450 enzymes and the interaction with efflux transporters were conducted.

Rifaximin is practically insoluble in water and poorly absorbed after oral administration, thus it is intended to be used locally to treat disease conditions where the desired site of action is the gastrointestinal tract.

4.2.1 Mechanism of Action

Rifaximin is a non-aminoglycoside, semisynthetic antibiotic derived from Rifamycin that has antimicrobial activity against Gram-positive, Gram-negative, aerobic, and anaerobic enteric bacteria similar to its parent compound. Rifaximin acts primarily by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase, resulting in inhibition of bacterial RNA synthesis

4.2.2 Pharmacodynamics

Rifaximin is presumably acting locally; therefore, the systemic exposure is considered more relevant to safety than efficacy. The concentration-response relationship was not studied.

See Section 5, on page 20, for discussion of dose response relationship with efficacy.

Dose response for Safety:
There was no dose-related increase in treatment-emergent adverse events (TEAE) in the total daily dose ranging from 550 mg to 2200 mg (Table 2). The most common AE experienced during the overall evaluation period were headache (all rifaximin 5%, placebo 6%), nausea (4%, 4%), diarrhea (3%, 3%), and urinary tract infection (3%, 2%).

4.2.3 Pharmacokinetics

When rifaximin was orally administered, less than 1% of the administered dose is systemically absorbed. About 0.32% of the administered dose was recovered in urine, of which 0.03% of the administered dose was present as rifaximin, indicating absorbed rifaximin undergoes substantial metabolism. An in vitro study showed that rifaximin is a substrate of efflux transporter(s), including p-glycoprotein. In vitro studies using inside-out membrane vesicles expressing transporter(s) suggest that rifaximin inhibits substrate transport by transporters especially MDR1 (p-gp) and MRP2. Further studies are warranted to assess in vivo drug interaction potential via interaction with transporters.

The mean Cmax and mean AUC after 550mg rifaximin three times daily dosing was highly variable and approximately 1.7-fold higher in IBS subjects than in healthy volunteers. The higher rifaximin plasma level in subjects with IBS might be attributed to

altered intestinal permeability in IBS. Concomitant rifaximin slightly reduced the systemic exposure of oral contraceptive by 4-14%.

In vitro studies suggest that rifaximin is metabolized mainly by CYP3A4, and that CYP isoforms such as 2C8, 2C9, 2C19 and 2D6 are also involved in metabolism of rifaximin but to a lesser degree. The effect of concomitant CYP3A4 inhibitor(s) on rifaximin systemic exposure was not studied in vivo.

In vitro studies have shown that rifaximin did not inhibit cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, and CYP3A4 at concentrations up to 200 ng/ml. The highest plasma concentration of rifaximin observed was 66 nM (52.2 ng/ml) in patients with severe hepatic impairment. As such in vivo drug interaction via inhibition of CYP enzymes by rifaximin appears to be low.

4.3 Clinical Microbiology

Public Heath and Antibiotic Resistance

The Division is concerned about the approval of a broad spectrum antibiotic in a large population without a proven or strongly suspected infection caused by bacteria, as per current best practice guidelines and the serious public health consequences of the development of resistance. Therefore, the Division of Special Pathogens and Transplant Products was consulted, and they responded that the clinical data are insufficient to assess the potential negative public health impact of rifaximin on the development of antibacterial resistance.

Minimum inhibitory concentrations (MIC) breakpoints for rifaximin have not been officially defined as the drug is not systemically absorbed to any great extent and local concentrations of rifaximin at the site of infection in the gastrointestinal tract are difficult to measure. Increased MICs in coliform bacteria were not observed in a clinical trial of college students treated with rifaximin for three days for travelers' diarrhea, i.e. rifaximin MICs in coliform bacteria remained the same pre- and post-therapy.

Division of Special Pathogens and Transplant Products (DSPTP) stated that repeated courses of any antibacterial drug in a population will eventually result in some degree of increase in minimum inhibitory concentrations (MICs) of the antibacterial and in clinical failures. If rifaximin provides marginal clinical improvement in non-constipating IBS then the potential risk of rifaximin resistance and cross-resistance with other rifamycins (e.g. rifampin) in GI flora and in other bacteria becomes more important because the benefit obtained may not outweigh this risk.

The question of whether the mutations related to rifamycin resistance could be seen long-term in tuberculosis (*Mycobacterium tuberculosis*) or MAC (*Mycobacterium avium* complex) infection should be considered but is not of major concern. *M. tuberculosis*

and *M. avium* are not normal gut flora and the IBS patients are not more at risk of acquiring tuberculosis or MAC infection than the general population Gene mutations are more likely to be related to systemically absorbed rifamycins such as rifampin and rifabutin used to treat mycobacterial disease.

Microbiological testing of stool samples for the development of antibiotic resistance
The DSPTP has provided input to the applicant on the design of the Post Marketing Trials to evaluate the safety of rifaximin for Hepatic Encephalopathy.

- The method used to detect *C. difficile* toxin in patients prior to randomization should be an FDA cleared method. If not the details of the method and performance characteristics of the test in the laboratory where testing will be performed should be provided for review. It was recommended that a test cleared by the FDA should be used to identify the presence of the toxin. This will alleviate the need to validate the test method.
- Methods for stool specimen collection, specimen identification, shipping and processing should be submitted for review prior to study initiation. Stools should be cultured to allow for isolation of *C*. *difficile* and the detection of overgrowth of bacteria and yeast.
- Information on the methods for culture, species identification, and in vitro susceptibility testing of antimicrobial agents, including rifaximin and rifampin against *C. difficile* and predominating bacteria, should be submitted for review. In vitro susceptibility testing should be done using standard methods, such as described by Clinical and Laboratory Standards Institute.
- All isolates should be identified by well recognized methods.
- Name and location of microbiology laboratory or laboratories where stool specimens will be cultured and tested should be identified.

5 Analysis of Dose Ranging Trial and Dose Selection

5.1 Summary

The applicant performed a phase 2 dose ranging trial (Study RFIB2001), in which three dose levels of rifaximin were evaluated: 275 mg, 550 mg and 1100 mg twice daily (550, 1100, and 2200 mg daily, respectively). The applicant examined two durations of treatment, two weeks and four weeks, at the 550 mg dose level. The results favored the 550 mg dose of rifaximin over the two other dose levels (including the higher dose) and placebo. No treatment benefit was seen with the longer treatment period. Subsequently, for the phase 3 trials the applicant chose to increase the dosing frequency to three times daily (i.e., 550mg three times daily, with a total daily dose of 1650 mg) in the phase 3 trials. Because only one dose level was studied for three times

daily dosing frequency, the dose-response with this dosing frequency has not been adequately established. Examination of the literature and the references the applicant cited showed those trials were performed with 7 and 10 days dosing duration, and the efficacy results evaluated were improvement of IBS symptoms and/or normalization of breath test. The applicant did not examine any treatment period shorter than 2 weeks.

5.2 Trial Design

Study RFIB2001 was a phase 2b, multicenter, randomized, double-blind, placebo-controlled, dose ranging study designed to assess the efficacy and safety of 3 different doses (275, 550, and 1100 mg) of rifaximin administered BID for either 2 or 4 weeks in subjects with IBS-D. Two co-primary efficacy endpoints were evaluated: adequate relief of global IBS symptoms and adequate relief of IBS bloating at the end of the 4-week treatment phase (for at least 2 of the final 3 weeks).

5.3 Baseline Characteristics

Baseline IBS disease characteristics were generally comparable between study RFIB2001 and the subsequent phase 3 trials. In RFIB2001, IBS symptoms were comparable among the 4 rifaximin treatment groups and the placebo group at baseline; no statistically significant differences were observed and there were no notable between-group differences for any category. Randomized subjects had IBS confirmed by Rome II criteria, and consistent with the study design, most subjects (> 85%) had IBS-D at baseline. Approximately 14% of participating subjects had IBS-A, IBS-C, or other (undefined).

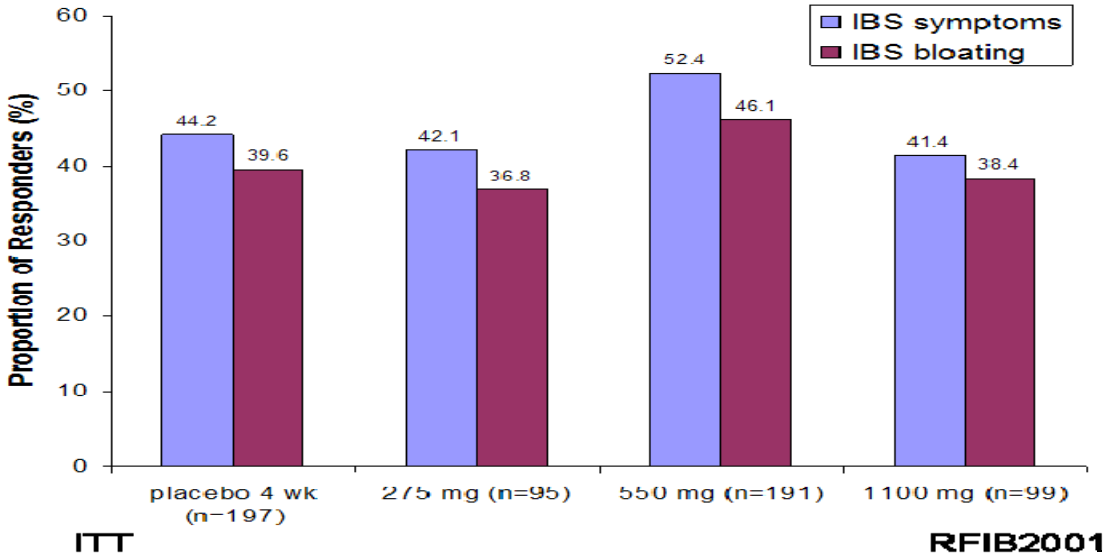
5.4 Demographic characteristics

Demographic characteristics for IBS subjects in RFIB2001 were very similar to those observed in the phase 3 IBS trials. In the ITT population, median age was 46 years (min-max: 19-82 years). Most subjects were white (93.1%), and the majority were female (75.3%). Demographics were comparable among treatment groups.

5.5 Efficacy Analysis

The efficacy analyses in the 550 mg BID x2 weeks rifaximin group (N=191) versus the placebo group (N=197) of the co-primary endpoints, adequate relief of global IBS symptoms (52% vs. 44%, p = 0.0314) and adequate relief of IBS bloating (46% vs. 40%, p = 0.0402) demonstrated that there were higher proportions of rifaximin subjects with responses than placebo subjects. In an analysis of the co-primary endpoints by study week, the superiority of the rifaximin 550 mg BID 2 week group over placebo with regards to adequate relief of global IBS symptoms and IBS bloating was maintained during the 12-week post-treatment follow-up in this trial.

Figure 2: Adequate relief of IBS symptoms and bloating after 2 week treatment with 275, 550, and 1100 mg rifaximin twice daily



Reviewer's Comments
In this study, there was no obvious dose-response relationship for efficacy among doses 275, 550, or 1100 mg given twice daily, although 550 mg BID appeared to be more effective than placebo for both co-primary endpoints. Notably there was a significant placebo effect, with a response rate of 40-45% for both co-primary endpoints (i.e. adequate relief from global IBS symptoms and the symptom of IBS-related bloating). The rifaximin 275 mg BID (550 mg daily) and 1100 mg BID (2200 mg daily) regimens were associated with response rates similar to placebo.

5.6 Justification for Dose Selection for Trials

Applicant
The selected dose regimen of 1650 mg/day (550 mg TID) for 14 days was primarily based on results from the Salix phase 2 IBS trial (RFIB2001), findings from a Salix scintigraphy study (RFPK1002), and review of the published literature for rifaximin treatment in IBS and SIBO.

The Salix phase 2 study (RFIB2001), described above, demonstrated efficacy in the co-primary endpoints of improvement in IBS symptoms and improvement in IBS bloating with 550 mg BID dosing versus placebo after 14 days of rifaximin treatment. Secondary analyses of IBS daily symptoms also suggested improvement in bloating

and abdominal pain/discomfort in the 1100 mg BID group versus placebo. Additionally, rifaximin was generally well tolerated in each of the 4 rifaximin treatment arms.

A Salix scintigraphy study (RFPK1002) conducted with 19 healthy males revealed a rapid GI transit time of rifaximin (200 mg tablets). Initial disintegration of the tablets occurred in the stomach between 6 and 23 minutes post-dose, while the initial small intestinal transit time was between 3y82 and 6.25 hours. Considering this rapid transit time, it was thought that TID dosing would maintain a higher continuous intestinal lumen concentration of rifaximin to inhibit the bacteria responsible for IBS symptoms. Also, there was support for TID dosing in a published study comparing rifaximin treatment with placebo using a 400 mg TID regimen (1200 mg daily dose) in adult subjects with IBS. In this literature report of a trial of 87 subjects, rifaximin treatment (400 mg TID; n = 43) resulted in greater improvement in IBS symptoms (p = 0.02) and IBS bloating (p = 0.01) over 10 weeks of treatment follow-up compared with placebo (n = 44), according to the investigators published report (these data have not been confirmed by the Agency).

The use of a higher daily dose of rifaximin for IBS is also rationalized by findings from 2 dose-ranging studies in the literature for rifaximin treatment in SIBO. In these trials, rifaximin was more effective in eradicating SIBO (diagnosed by breath testing in patients with IBS) at progressively higher doses without a concurrent increase in side effects of the study drug. In a randomized trial of 80 subjects, rifaximin at 1600 mg/day demonstrated higher efficacy in treatment of SIBO compared with 1200 mg/day.[12] In a study evaluating 90 subjects, rifaximin was more effective in eradicating SIBO with a daily dose of 1200 mg compared with daily doses of 600 mg and 800 mg.[13] These uncontrolled trials did not report any significant differences between treatment groups with respect to subject compliance and recorded side effects.

In summary, the findings that support the selected dose regimen of 1650 mg/day (550 mg TID) are the following:

- Results of IBS phase 2 trial RFIB2001 showing efficacy at the rifaximin 550 mg BID dose and results favoring 1100 mg BID for bloating and abdominal pain endpoints,
- Results of scintigraphy study RFPK1002 suggesting that TID dosing should maintain a higher gut concentration of rifaximin than BID dosing,
- Results of a published IBS study that indicate efficacy in subjects who received rifaximin by TID dosing,[14] and
- Results literature reports from dose-ranging studies in patients with a diagnosis of SIBO by breath testing, which showed increasing efficacy at progressively higher rifaximin doses (doses ranged from 600 mg/day to 1600 mg/day).

Reviewer's Comments

Although the applicant rationalized a higher daily dose of 1650 mg (550 mg TID) based on published studies mentioned above, there was no obvious benefit of a higher daily dose between the total daily doses 1100 mg and 2200 mg administered in two divided doses.

Although the applicant rationalized the dosing frequency change from twice daily to three times a day to maintain high initial concentration of rifaximin in small intestine based on initial intestinal transit time of 3-6 hours determined in healthy subjects, it is unknown how the intestinal transit time of rifaximin in healthy subjects compares to a patient population who has altered intestinal motility. Dose-response relationship was not explored in the three times daily regimen in this clinical development program.

During a phase 2 trial, the treatment effect of a 4 week treatment was compared with that of 2 week treatment at 550 mg dose level. The 4 week treatment was not associated with a greater treatment effect than placebo. Treatment duration shorter than 2 weeks was not studied in this clinical development program.

6 Phase 3 Trial Design

The applicant submitted data from two identically designed phase 3, randomized, controlled, multicenter, clinical trials; RFIB3007 and RFIB3008. Section 6, on page 25 will present the trials design for both trials. Section 7, on page 28 will present an efficacy summary for both trials. Section 8, on page 29 will present data from the RFIB3007 and Section 9, on page 37 will present the data from RFIB3008.

6.1 Methods

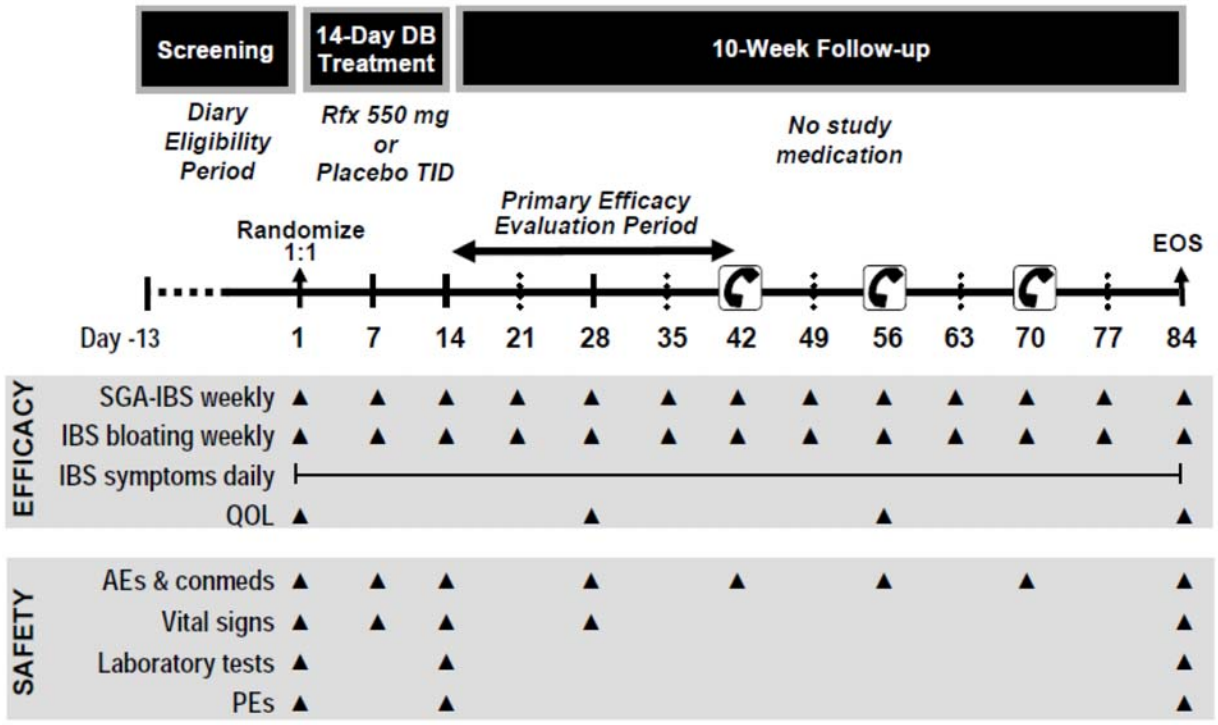
There was a 14-day treatment phase and a 10-week follow-up phase without treatment in these phase 3, multi-center, randomized, double-blind, placebo-controlled trials of rifaximin in subjects with non-constipation IBS. Approximately 600 eligible subjects were planned to be randomized in a 1:1 ratio to receive either rifaximin 550 mg TID or placebo TID.

The study consisted of the following phases:
Screening phase - Prospective subjects were required to undergo screening procedures including informed consent, screening assessments (e.g., colonoscopy, if necessary), and completion of the diary eligibility phase. The diary eligibility phase began no earlier than 7 days after the colonoscopy and within 10 ± 3 days prior to randomization (the duration of the diary eligibility phase was ≥ 7 days). During the diary eligibility phase, subjects were required to respond to SGA questions (yes/no) and daily IBS symptom-related questions (using a 7-point Likert scale) for at least 7 days in the Interactive Voice Response System (IVRS).

Treatment phase (Days 1 to 14 + 2) - Starting on Day 1 (randomization visit), eligible subjects received blinded study drug according to the randomization schedule for 14 days. Interim clinic visits occurred at Week 1 (Day 7 ± 1) and Week 2 (Day 14 + 2). Subjects were instructed to continue to record their daily IBS symptoms and weekly SGA responses in the IVRS.

Follow-up phase without treatment (from completion of treatment to Day 84 ± 3 [Week 12]) - Randomized subjects were followed after completion of treatment for 10 additional weeks. No study treatment was administered during the follow-up phase. Interim clinic visits occurred at Week 4 (Day 28 ± 3) and Week 12 (termination visit; Day 84 ± 3). In addition, telephone contacts occurred at Weeks 6 (Day 42 ± 3), 8 (Day 56 ± 3), and 10 (Day 70 ± 3). Subjects were instructed to continue to record their daily IBS symptoms and weekly SGA responses in the IVRS.

Figure 3: Trial Design



Abbreviations: AE = adverse event; Conmeds = concomitant medications; IBS = irritable bowel syndrome; IVRS = interactive voice response system; PE = physical examination; RFX = rifaximin; SGA = Subject Global Assessment; TID = 3 times daily

Reviewer's Comments:
The design of this trial is unusual for IBS drugs in that all previous drugs approved for IBS, which have a different mechanism of action from rifaximin (i.e., affect motility), were used for the entire length of the trial. Rifaximin was administered for 14 days only and then discontinued. The applicant elected to define the primary and key secondary endpoint by using a Primary Efficacy Period of the four weeks following the treatment period (weeks 3 thru 6). IBS drugs have not been previously approved with this short efficacy period. The Applicant was advised at the end-of-phase 2 meeting that the trial should be 12 weeks in length and that efficacy should be assessed at week 4, 8 and 12. The choice of a shorter efficacy time period is important in the discussion of efficacy.

6.2 Endpoints

The primary efficacy endpoint was the proportion of subjects who achieved adequate relief of global IBS symptoms (i.e., responders) for at least 2 of 4 weeks during the PEP (i.e., Weeks 3 through 6 [Days 15-42]). Adequate relief of global IBS symptoms was defined as a response of "yes" to the following weekly (every 7 days) SGA question: "In regards to your IBS symptoms, compared to the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms? [Yes/No]"

The key secondary efficacy endpoint was the proportion of subjects who achieved adequate relief of bloating (i.e., responders) for at least 2 of 4 weeks during the PEP (i.e., Weeks 3 through 6 [Days 15-42]). Adequate relief of bloating was defined as a response of "yes" to the following weekly (every 7 days) question: *"In regards to your IBS symptom of bloating, compared to the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptom of bloating? [Yes/No]"*

Medical Officer's Comments:
Note that all the endpoints are evaluated only during the PEP which is limited to Weeks 3 thru 6. In addition the endpoints require patients to compare how they presently feel to how they felt in the past which introduces recall bias.

In recognition of the limitations of using a single-item patient-reported rating of change as a primary endpoint and based on the principles explained in the PRO guidance, we now recommend the development of a multi-item PRO instrument that captures all of the clinically important signs and symptoms of IBS. Prospectively defined changes in the scores measured by this PRO instrument between treatment arms should be used as the primary endpoint in IBS clinical trials. The instrument should be population specific (i.e., developed for use in IBS-C or for use in IBS-D).

7 Summary of Efficacy Results

The applicant performed two identically designed phase 3 trials (RFIB3007 and RFIB3008) with a dose of 550mg three times daily (1650mg per day), for a two week treatment period. The trials were both double blinded, placebo-controlled, randomized, multi-center 12-week trials preformed in the United States primarily with a few sites in Canada. Each trial included over 600 patients, with a two week screening period followed by a two week treatment period and an additional 10 weeks of evaluation. The trials excluded patients with severe symptoms and only included patients with IBS-D. There was no long-term follow-up.

The primary endpoint was the proportion of subjects who achieved adequate relief of global IBS symptoms during the Primary Evaluation Period (PEP); which was defined as Weeks 3 through 6. Patients were asked the question "*In regards to your IBS symptoms, compared to the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms?"* These data were to be entered by the patient at the end of each **week** using an IVRS system. The patients also recorded a **daily** IVRS diary for collection of data for other secondary and exploratory endpoints. The key secondary endpoint was the proportion of subjects who achieved adequate relief of bloating during the PEP (2 of 4 weeks).

The efficacy results for the primary endpoint (during PEP) showed a delta (between rifaximin and placebo) favoring rifaximin: 10% in RFIB3007 and 9% in RFIB3008. Similar efficacy was seen for the key secondary endpoint, with a delta favoring rifaximin: 11% in RFIB3007 and 9% in RFIB3008. The FDA-requested exploratory endpoint defined by abdominal pain and stool consistency showed a delta favoring rifaximin: 8% in RFIB3007 and 11% in RFIB3008. These deltas are within the ranges observed in comparisons to placebo in the trials that supported registration of previously approved IBS drugs; however, historically a 12-week efficacy period has been used, not just Weeks 3 thru 6.

Durability of Response

The applicant presented analyses that appeared to show that treatment was effective for the entire length of the 12-week trial; however the choice of statistical analysis allowed the p-value to be driven by the treatment group difference in number of patients with no treatment effect (0 months of efficacy) and may be misleading. Therefore the FDA reviewers elected to perform exploratory analyses using definitions for overall responder that had been used for previous IBS drug approvals and using the responder definition from the FDA draft guidance for IBS drug trial design.

Defining a monthly responder as a subject with at least two of four weeks of response in that month, and an overall responder defined as a monthly responder for at least 2 of the 3 months of the trial, the results do not meet statistical significance for both trials

RFIB3007 and RFIB3008 for the primary endpoints of global IBS symptoms. Only trial RFIB3008 achieves significance for the prespecified "key" secondary endpoint of bloating. See Table 5 on page 36.

When the data were analyzed by week and using an overall responder redefined as a subject in response for at least 50% of the weeks of the trial (as per the present Guidance), results failed to meet statistical significance for 7 of the 12 weeks of the trial. See Table 6 on page 36.

The results of the weekly responder analysis indicate that efficacy lasts only for the first 4 weeks after treatment, then decreases after the sixth or seventh week.

8. Phase 3 Efficacy Results Trial RFIB 3007

8.1 Demographics

In the ITT population, the median age of subjects was 46 years (min-max: 18-86 years). Most subjects were white (90%), and the majority were female (73%). Demographic characteristics were comparable between treatment groups.

Table 1: Demographic Characteristics by Treatment Group (ITT Population) RFIB3007

Characteristic Category or statistic	Rifaximin 550 mg TID N = 309	Placebo N = 314	All Treatments N = 623
Age (years)			
Mean (SD)	46.2 (14.97)	45.5 (14.58)	45.8 (14.77)
Median (minimum, maximum)	46.0 (18, 86)	45.0 (18, 82)	46.0 (18, 86)
Sex – n (%)			
Male	74 (24)	92 (29)	166 (27)
Female	235 (76)	222 (71)	457 (73)
Race[a] – n (%)			
American Indian/Alaskan Native	2 (0.6)	0	2 (0.3)
Asian	2 (0.6)	1 (0.3)	3 (0.5)
Black/African American	24 (8)	30 (10)	54 (9)
Native Hawaiian/Pacific Islander	0	1 (0.3)	1 (0.2)
White	281 (91)	280 (89)	561 (90)
Other	0	2 (1)	2 (0.3)
Body Mass Index – kg/m^2			
Mean (SD)	29.53 (7.000)	28.76 (6.875)	29.14 (6.943)
Median (minimum, maximum)	28.20 (16.2, 60.7)	27.55 (17.2, 58.0)	27.90 (16.2, 60.7)

Source: Summary Table 14.1.2, Section 14.1; corresponding Data Listing 16.2.4.1, Appendix 16.2.4.
Abbreviations: ITT = intent to treat; SD = standard deviation; TID = 3 times daily.
a Subjects who checked > 1 race category on the case report form were classified as "Other."

8.2 Baseline Characteristics

At baseline, mean scores for IBS symptoms, IBS-related bloating, and IBS-related abdominal pain and discomfort were each > 3; mean score for stool consistency was 3.92, and subjects felt urgency associated with > 80% of their bowel movements during the screening phase.

Baseline IBS characteristics and symptoms scores were similar between treatment groups in the ITT population. All subjects had diarrhea-predominant, as determined using Rome II criteria.

Medical Officer's Comments:
The trial enrolled only IBS-D patients; no IBS-A patients were enrolled. Therefore, an indication for treatment of a non-C IBS population is not supported. The entry criteria also excluded patients with severe abdominal pain (> 4.5 on scale of 0 to 6) or severe bloating; therefore, the trial included only patients with mild to moderate disease.

Baseline Characteristics were balanced between treatment groups and were supportive of mild to moderate IBS-D symptoms, excluding patients with severe symptoms. Of the patients enrolled 88% were less than 65 years old, 72% were female, and 91% were white.

Table 2: Baseline IBS Characteristics and Symptom Scores by Treatment Group (ITT Population) RFIB3007

IBS Characteristics and Symptom Scores at Baseline	Rifaximin 550 mg TID N = 309	Placebo N = 314	All Treatments N = 623
IBS characteristics			
Time since first experienced onset of IBS symptoms, years			
Mean (SD)	11.89 (10.524)	11.42 (11.890)	11.65 (11.226)
Median (minimum, maximum)	9.06 (0.2, 52.9)	7.35 (0.2, 65.6)	8.20 (0.2, 65.6)
Time since diagnosis with IBS, years			
Mean (SD)	6.26 (7.874)	6.42 (9.245)	6.34 (8.586)
Median (minimum, maximum)	3.72 (0, 42.3)	3.21 (0, 59.3)	3.65 (0.0, 59.3)
IBS subtype			
Diarrhea predominant	309 (100)	314 (100)	623 (100)
Constipation predominant	0	0	0
Alternating	0	0	0
Symptom scores at baseline			
Average daily score of global IBS symptoms[a,b]			
Mean (SD)	3.35 (0.692)	3.39 (0.680)	3.37 (0.686)
Median (minimum, maximum)	3.33 (1.4, 5.3)	3.43 (1.8, 5.9)	3.38 (1.4, 5.9)
Average daily score of bloating[b,c]			
Mean (SD)	3.30 (0.763)	3.26 (0.728)	3.28 (0.746)
Median (minimum, maximum)	3.29 (1.0, 5.1)	3.25 (1.5, 5.3)	3.29 (1.0, 5.3)
Average daily score of abdominal pain[b,d]			
Mean (SD)	3.25 (0.700)	3.23 (0.724)	3.24 (0.712)
Median (minimum, maximum)	3.20 (1.3, 5.0)	3.29 (1.6, 4.7)	3.25 (1.3, 5.0)
Average daily score of stool consistency[e]			
Mean (SD)	3.90 (0.318)	3.93 (0.283)	3.92 (0.301)
Median (minimum, maximum)	3.88 (3.0, 5.0)	4.00 (3.3, 4.7)	3.89 (3.0, 5.0)
Percentage of time with stool urgency[f]			
Mean (SD)	81.80 (22.277)	82.92 (22.329)	82.36 (22.292)
Median (minimum, maximum)	87.50 (0, 100.0)	90.45 (0, 100.0)	88.89 (0,100.0)
Average daily bowel movements			
Mean (SD)	2.86 (1.342)	2.98 (1.410)	2.92 (1.377)
Median (minimum, maximum)	2.63 (0.3, 7.8)	2.86 (0.7, 12.6)	2.71 (0.3, 12.6)

Source: Summary Table 14.1.3, Section 14.1; corresponding Data Listing 16.2.4.2, Appendix 16.2.4.

Abbreviations: IBS = irritable bowel syndrome; ITT = intent to treat; SD = standard deviation; TID = 3 times daily.

a The question asked was "*In regards to all your symptoms of IBS; on a scale of 0-6, how bothersome were your symptoms of IBS today?*"

b Responses to the question were: 0 = not at all, 1 = hardly, 2 = somewhat, 3 = moderately, 4 = a good deal, 5 = a great deal, 6 = a very great deal.

c The question asked was "*In regards to your specific IBS symptom of bloating; on a scale of 0-6, how bothersome was your IBS-related bloating today?*"

d The question asked was "*In regards to your specific IBS symptom of abdominal pain and discomfort; on a scale of 0-6, how bothersome were your IBS-related abdominal pain and discomfort today?*"

e Responses to the question "What was the overall stool form of your bowel movements today?" were 1 = very hard, 2 = hard, 3 = formed, 4 = loose, 5 = watery.

f Calculated as 100 * (number of days felt/experienced a sense of urgency with any of the bowel movements / number of days with bowel movements).

8.3 Subject Disposition

A total of 1112 subjects were assessed for study eligibility, and 623 subjects were randomized to the rifaximin (309 subjects) and placebo (314 subjects) groups. Of these 623 subjects, 607 (97%) completed the treatment phase (through Week 2 [Day 14]); 594 subjects (95%) completed the study through the end of the PEP (Week 6 [Day 42]); and 575 subjects (92%) completed the study (through Week 12 [Day 84]). Similar proportions of subjects in each treatment group completed the treatment phase (rifaximin 97%, placebo 98%), completed through Week 6 (rifaximin 96%, placebo 95%), and completed the study (rifaximin 92%, placebo 93%). Forty-eight of 623 subjects (8%) discontinued early from the study. Primary reasons for early discontinuation were subject request (8 in each group); AEs or loss to follow up (each for 8 subjects rifaximin, 7 subjects placebo); and noncompliance or pregnancy (each for 1 subject rifaximin and none in placebo).

Table 3: Subject Disposition by Treatment Group (All Randomized Subjects) – RFIB3007

Disposition Parameter	Rifaximin 550 mg TID n (%)	Placebo n (%)	All Treatments n (%)
Subjects randomized (N)	309	314	623
ITT population[a]	309 (100)	314 (100)	623 (100)
PP population[b]	294 (95)	300 (96)	594 (95)
Subjects completed the treatment phase (through Week 2 [Day 14])	301 (97)	306 (98)	607 (97)
Subjects completed through Week 6 (Day 42)	295 (96)	299 (95)	594 (95)
Subjects completed the study (through Week 12 [Day 84])	283 (92)	292 (93)	575 (92)
Subjects discontinued study early	26 (8)	22 (7)	48 (8)
Primary reason for early discontinuation:			
Adverse event/serious adverse events	8 (3)	7 (2)	15 (2)
Subject request	8 (3)	8 (3)	16 (3)
Lost to follow-up	8 (3)	7 (2)	15 (2)
Noncompliance	1 (0.3)	0	1 (0.2)
Pregnancy	1 (0.3)	0	1 (0.2)

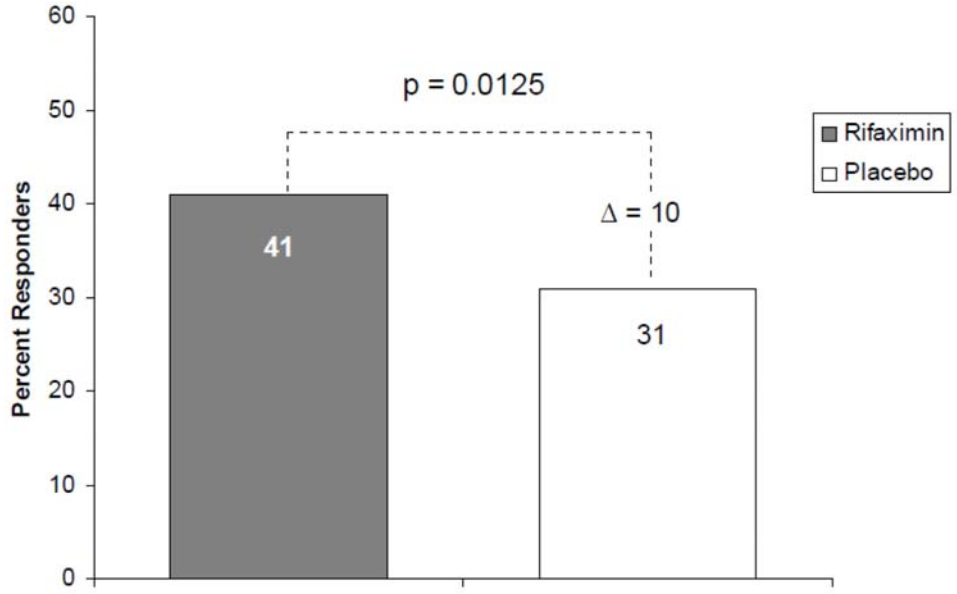
Source: Summary Table 14.1.1a, Section 14.1; corresponding Data Listing 16.2.1, Appendix 16.2.1.
Abbreviations: ITT = intent-to-treat; PP = per-protocol; TID = 3 times daily.
a The ITT population included all randomized subjects who ingested at least 1 dose of study drug.
b The PP population excluded all ITT subjects who failed to meet inclusion criterion 4 (IBS symptoms) or 5 (inadequate relief), met exclusion criterion 1 (had constipation IBS) or 8 (had positive stool test for exclusionary flora), or had documented evidence of bipolar disorder.

8.4 Analysis of Primary Endpoint RFIB3007

Adequate relief of global IBS symptoms was reported by a greater proportion of rifaximin subjects (41%) than placebo subjects (31%) (p = 0.0125) in the ITT population,

Reviewer's Comments:
The trial did meet statistical significance for the primary endpoint during the PEP time frame, with a delta between treatment and placebo groups of 10%. This treatment difference is within the range of treatment difference observed in trials that supported prior IBS drug approvals.

Figure 4: Percentage of Responders for the Primary Endpoint by Treatment Group (ITT Population) – RFIB3007



Source: Summary Figure 14.2.1.1a and Table 14.2.1a (Section 14.2); corresponding Data Listings 16.2.6.1 and 16.2.6.3 (Appendix 16.2.6)

Notes: Subjects were responders if they answered "Yes" to the weekly SGA question, *"In the past 7 days, have you had adequate relief of your IBS symptoms?"* for at least 2 of 4 weeks during the PEP (ie, Weeks 3 through 6 [Days 1-42]), without requiring antibiotics or >2 doses of prohibited medications (subjects were considered nonresponders from the date of the introduction of the antibiotics or prohibited medication, regardless of their actual response data).
The p-value was obtained from a logistic regression model with fixed effects for treatment arm and analysis center.

8.5 Exploratory Analysis - Sustained Efficacy Evaluation - Primary Endpoint – RFIB3007

Medical Officers Comments:
*The applicant presented exploratory analyses that appeared to show that treatment was effective for the entire length of the 12-week trial (*Table 4 *on page 35); however the choice of statistical analysis allowed the p-value to be driven by the treatment group difference in number of patients with no treatment effect (0 months of efficacy) and may be misleading. Therefore, the FDA reviewers elected to perform exploratory analyses using definitions for overall responder that had been used for previous IBS drug approvals and using the responder definition from the FDA draft guidance for IBS drug trial design.*

*Defining a monthly responder as a subject with at least two of four weeks of response in that month, and an overall responder defined as a monthly responder for at least 2 of the 3 months of the trial; the results do not meet statistical significance for trial RFIB3007 for the primary endpoint of global IBS symptoms The results fail at month two and month three, with an overall treatment difference of 4.7% (p=0.217), (*Table 5 *on page 36).*

*When the data were analyzed by week and using an overall responder redefined as a subject in response for at least 50% of the weeks of the trial (as per the present Guidance), the results showed efficacy for only week two thru week six, which is less then 50% of the weeks. The overall treatment difference was 6.0% (p=0.1073). Efficacy was observed during the PEP (*Table 6 *on page 36).*

Table 4: Number of Months of Adequate relief of Global IBS Symptoms Based on Weekly SGA Assessments (ITT Population) RFIB3007

	Rifaximin 550 mg TID N = 309 n (%)	Placebo N = 314 n (%)
Number of Months Subject had Adequate Relief of Global IBS Symptoms		
During Month 1		
0	168 (54)	203 (65)
1	141 (46)	111 (35)
	Odds ratio = 1.55 95% CI = 1.12 to 2.15 p = 0.0081	
During Month 1 plus Month 2		
0	156 (51)	180 (57)
1	54 (18)	62 (20)
2	99 (32)	72 (23)
	Odds ratio = 1.41 95% CI = 1.04 to 1.91 p = 0.0260	
During Months 1, 2, and 3		
0	150 (49)	174 (55)
1	50 (16)	44 (14)
2	30 (10)	38 (12)
3	79 (26)	58 (19)
	Odds ratio = 1.35 95% CI = 1.00 to 1.82 p = 0.0477	

Source: Summary Table 14.2.5a (Section 14.2); corresponding Data Listings 16.2.6.1 and 16.2.6.4 (Appendix 16.2.6).
Abbreviation: CI = confidence interval.
Notes: A subject achieved adequate relief if he/she answered "Yes" to the weekly SGA question for ≥ 2 weeks per month. Subjects who received antibiotics or > 2 doses of prohibited medications were entered as nonresponders from time of beginning the medications, regardless of the actual response data.
The p-value and odds ratio were obtained using the proportional odds model for ordinal outcome with fixed effects for treatment arm and analysis center.

Table 5: Monthly Responder Rate of Adequate Relief of IBS Symptoms by Treatment Group (LOCF, ITT)

Study 3007				
	Placebo	**Rifaximin**	**Difference (Rifaximin-Placebo)**	**Chi-square p-value**
Month 1	111/314 (35.4%)	141/309 (45.6%)	10.2%	0.0089
Month 2	95/314 (30.3%)	111/309 (35.9%))	5.6%	0.1327
Month 3	88/314 (28.0%)	95/309 (30.7%)	2.7%	0.4563

Table 6: Weekly Responder Rate of Adequate Relief of IBS Symptoms by Treatment Group

Study 3007				
	Placebo	**Rifaximin**	**Difference (Rifaximin-Placebo)**	**Chi-square p-value**
Week 1	93/310 (30.0%)	110/303 (36.3%)	6.3%	0.0973
Week 2	101/304 (33.2%)	126/298 (42.3%)	9.1%	0.0219
Week 3	95/303 (31.4%)	117/297 (39.4%)	8.0%	0.0394
Week 4	86/302 (28.5%)	113/296 (38.2%)	9.7%	0.0119
Week 5	83/301 (27.6%)	109/295 (37.0%)	9.4%	0.0143
Week 6	84/299 (28.1%)	107/295 (36.3%)	8.2%	0.0329
Week 7	87/299 (29.1%)	102/295 (34.6%)	5.5%	0.1517
Week 8	82/299 (27.4%)	90/295 (30.5%)	3.1%	0.4074
Week 9	81/299 (27.1%)	86/295 (29.2%)	2.1%	0.5762
Week 10	86/299 (28.8%)	82/295 (27.8%)	-1.0%	0.7938
Week 11	72/299 (24.1%)	84/295 (28.5%)	4.4%	0.2237
Week 12	81/299 (27.1%)	89/295 (30.2%)	3.1%	0.4064

Compiled by the statistical reviewer from sponsor's data dated 9/15/10
P-values were obtained by Chi-square test.

9 Phase 3 Efficacy Results – Trial RFIB3008

9.1 Demographics

In the ITT population, the median age of subjects was 46 years (min-max: 18-88 years). Most subjects were white (92%), and the majority were female (71%). Demographic characteristics were comparable between treatment groups.

Table 7: Demographic Characteristics by Treatment Group - RFIB3008

Characteristic Category or statistic	Rifaximin 550 mg TID N = 315	Placebo N = 320	All Treatments N = 635
Age (years)			
Mean (SD)	45.9 (13.87)	46.3 (14.57)	46.1 (14.22)
Median (minimum, maximum)	45.0 (19, 88)	46.0 (18, 82)	46.0 (18, 88)
Sex – n (%)			
Male	88 (28)	95 (30)	183 (29)
Female	227 (72)	225 (70)	452 (71)
Race[a]			
American Indian/Alaskan Native	1 (0.3)	2 (0.6)	3 (0.5)
Asian	6 (2)	2 (0.6)	8 (1)
Black/African American	21 (7)	14 (4)	35 (6)
Native Hawaiian/Pacific Islander	3 (1)	0	3 (0.5)
White	282 (90)	302 (94)	584 (92)
Other	2 (0.6)	0	2 (0.3)
Body Mass Index – kg/m^2			
Mean (SD)	28.92 (6.872)	28.80 (6.546)	28.86 (6.705)
Median (minimum, maximum)	27.80 (17.3, 55.8)	27.60 (15.7, 55.7)	27.70 (15.7, 55.8)

Source: Summary Table 14.1.2, Section 14.1; corresponding Data Listing 16.2.4.1, Appendix 16.2.4.
Abbreviations: ITT = intent to treat; SD = standard deviation; TID = 3 times daily.
a Subjects who checked > 1 race category on the case report form were classified as "Other."

9.2 Baseline Characteristics

At baseline, mean scores for IBS symptoms, IBS-related bloating, and IBS-related abdominal pain and discomfort were each > 3; mean score for stool consistency was 3.91, and subjects felt urgency associated with > 80% of their bowel movements during the screening phase. Baseline IBS characteristics and symptoms scores were similar between treatment groups in the ITT population. All subjects had diarrhea-predominant IBS, as determined using Rome II criteria. There were no notable differences in medical history between the rifaximin and placebo treatment groups.

Table 8: Baseline IBS Characteristics by Treatment Group (ITT Population) RFIB3008

IBS Characteristics and Symptom Scores at Baseline	Rifaximin 550 mg TID N = 315	Placebo N = 320	All Treatments N = 635
IBS characteristics			
Time since first experienced onset of IBS symptoms, years			
Mean (SD)	10.75 (10.203)	11.84 (10.355)	11.30 (10.286)
Median (minimum, maximum)	7.62 (0.3, 58.9)	8.84 (0.4, 55.6)	8.04 (0.3, 58.9)
Time since diagnosis with IBS, years			
Mean (SD)	5.86 (7.721)	6.84 (8.307)	6.35 (8.030)
Median (minimum, maximum)	2.90 (0, 53.9)	3.39 (0, 40.9)	3.04 (0, 53.9)
IBS subtype, n (%)			
Diarrhea predominant	315 (100)	320 (100)	635 (100)
Constipation predominant	0	0	0
Alternating	0	0	0
Symptom scores at baseline			
Average daily score of IBS symptoms[a,b]			
Mean (SD)	3.42 (0.712)	3.39 (0.681)	3.41 (0.696)
Median (minimum, maximum)	3.44 (1.3, 5.4)	3.35 (1.6, 5.4)	3.43 (1.3, 5.4)
Average daily score of IBS-related bloating[b,c]			
Mean (SD)	3.23 (0.738)	3.29 (0.739)	3.26 (0.739)
Median (minimum, maximum)	3.29 (1.5, 4.8)	3.33 (1.6, 5.6)	3.33 (1.5, 5.6)
Average daily score of IBS-related abdominal pain and discomfort[b,d]			
Mean (SD)	3.29 (0.703)	3.27 (0.698)	3.28 (0.700)
Median (minimum, maximum)	3.29 (1.6, 5.4)	3.29 (0.6, 5.0)	3.29 (0.6, 5.4)
Average daily score of stool consistency[e]			
Mean (SD)	3.91 (0.282)	3.91 (0.310)	3.91 (0.296)
Median (minimum, maximum)	3.90(3.1, 4.7)	3.90(3.1, 5.0)	3.90(3.1, 5.0)
Percentage of time with stool urgency,[f] n (%)			
Mean (SD)	81.33 (22.762)	82.16 (22.495)	81.75 (22.614)
Median (minimum, maximum)	87.50 (8.3, 100.0)	89.44 (14.3, 100.0)	87.50 (8.3, 100.0)
Average daily bowel movements			
Mean (SD)	3.04 (1.572)	3.00 (1.530)	3.02 (1.550)
Median (minimum, maximum)	2.78 (0.7, 17.1)	2.78 (0.1,12.5)	2.78 (0.1,17.1)

Source: Summary Table 14.1.3, Section 14.1; corresponding Data Listing 16.2.4.2, Appendix 16.2.4.
Abbreviations: IBS = irritable bowel syndrome; ITT = intent to treat; SD = standard deviation; TID = 3 times daily.

a The question asked was "*In regards to all your symptoms of IBS; on a scale of 0-6, how bothersome were your symptoms of IBS today?*"

b Responses to the question were: 0 = not at all, 1 = hardly, 2 = somewhat, 3 = moderately, 4 = a good deal, 5 = a great deal, 6 = a very great deal.

c The question asked was "*In regards to your specific IBS symptom of bloating; on a scale of 0-6, how bothersome was your IBS-related bloating today?*"

d The question asked was "*In regards to your specific IBS symptom of abdominal pain and discomfort; on a scale of 0-6, how bothersome were your IBS-related abdominal pain and discomfort today?*"

e Responses to the question "What was the overall stool form of your bowel movements today?" were 1 = very hard, 2 = hard, 3 = formed, 4 = loose, 5 = watery.

f Calculated as 100 * (number of days felt/experienced a sense of urgency with any of the bowel movements / number of days with diary data).

9.3 Subject Disposition

A total of 1025 subjects were assessed for study eligibility, and 637 subjects were randomized to the rifaximin (316 subjects) and placebo (321 subjects) groups. Of these 637 subjects, 623 (98%) completed the treatment phase (through Week 2 [Day 14]); 615 subjects (97%) completed the study through the end of the PEP (Week 6 [Day 42]); and 603 subjects (95%) completed the study (through Week 12 [Day 84]). Similar proportions of subjects in each treatment group completed the treatment phase (rifaximin 98%, placebo 98%), completed through Week 6 (rifaximin 98%, placebo 96%), and completed the study (rifaximin 95%, placebo 94%). Thirty-four of 637 subjects (5%) discontinued early from the study. Primary reasons for early discontinuation were subject request (6 subjects rifaximin, 8 subjects placebo), lost to follow-up (6 subjects in each group), noncompliance (1 subject rifaximin, 2 subjects placebo), AEs (0 subjects rifaximin, 2 subjects placebo), and other (2 subjects rifaximin, 1 subject placebo).

Table 9: Subject Disposition by Treatment Group (All Randomized Subjects) RFIB3008

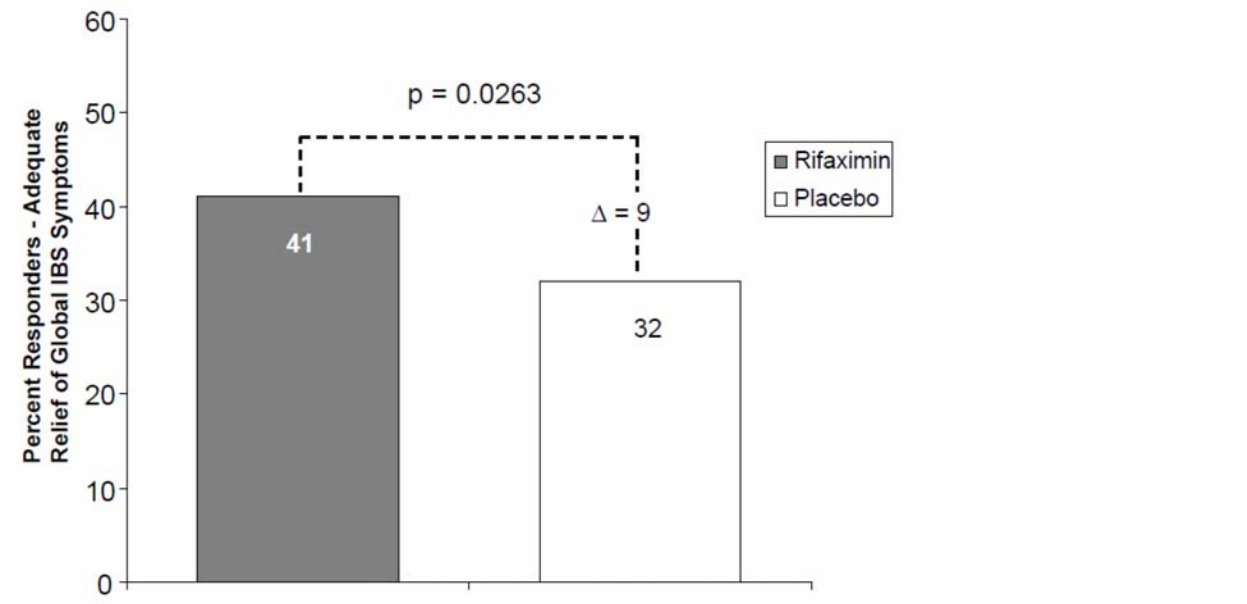
Disposition Parameter	Rifaximin 550 mg TID n (%)	Placebo n (%)	All Treatments n (%)
Subjects randomized (N)	316	321	637
ITT population[a]	315 (100)	320 (100)	635 (100)
PP population[b]	306 (97)	307 (96)	613 (96)
Subjects completed the treatment phase (through Week 2 [Day 14])	310 (98)	313 (98)	623 (98)
Subjects completed through Week 6 (Day 42)	308 (98)	307 (96)	615 (97)
Subjects completed the study (through Week 12 [Day 84])	301 (95)	302 (94)	603 (95)
Subjects discontinued study early	15 (5)	19 (6)	34 (5)
Primary reason for early discontinuation:			
Adverse event/serious adverse events	0	2 (0.6)	2 (0.3)
Subject request	6 (2)	8 (3)	14 (2)
Lost to follow-up	6 (2)	6 (2)	12 (2)
Noncompliance	1 (0.3)	2 (0.6)	3 (0.5)
Other[c]	2 (0.6)	1 (0.3)	3 (0.5)

Source: Summary Table 14.1.1a, Section 14.1; corresponding Data Listing 16.2.1, Appendix 16.2.1.
Abbreviations: ITT = intent-to-treat; PP = per-protocol; TID = 3 times daily.
a The ITT population included all randomized subjects who ingested at least 1 dose of study drug.
b The PP population excluded all ITT subjects who failed to meet inclusion criterion 4 (IBS symptoms) or 5 (inadequate relief), met exclusion criterion 1 (had constipation IBS) or 8 (had positive stool test for exclusionary flora), or had documented evidence of bipolar disorder.
c Other reasons for early discontinuation were randomization error: subject randomized although ineligible for the study (1123-0023 [placebo] and 1171-0002 [rifaximin]); and sponsor request: subject had to leave the vicinity of the site before completion of study (1166-0014 [rifaximin]).

9.4 Analysis of Primary Endpoint RFIB3008

Adequate relief of global IBS symptoms was reported by 41% of rifaximin subjects and 32% of placebo subjects (p = 0.0263) in the ITT population

Figure 5: Percentage of Responders for the Primary Endpoint by Treatment Group (ITT Population) RFIB3008



Source: Summary Figure 14.2.1.1a and Table 14.2.1a (Section 14.2); corresponding Data Listings 16.2.6.1 and 16.2.6.3 (Appendix 16.2.6)

Notes: Subjects were responders if they answered "Yes" to the weekly SGA question, *"In the past 7 days, have you had adequate relief of your IBS symptoms?"* for at least 2 of 4 weeks during the PEP (ie, Weeks 3 through 6 [Days 1-42]), without requiring antibiotics or >2 doses of prohibited medications (subjects were considered nonresponders from the date of the introduction of the antibiotics or prohibited medication, regardless of their actual response data).
The p-value was obtained from a logistic regression model with fixed effects for treatment arm and analysis center.

9.5 Sustained Efficacy – Primary Endpoint - Trial RFIB3008

Medical Officers Comments:
*The applicant presented exploratory analyses that appeared to show that treatment was effective for the entire length of the 12-week trial (*Table 10 *on page 42); however the choice of statistical analysis allowed the p-value to be driven by the treatment group difference in number of patients with no treatment effect (0 months of efficacy) and may be misleading. Therefore the FDA reviewers elected to perform exploratory analyses using definitions for overall responder that had been used for previous IBS drug approvals and using the responder definition from the FDA draft guidance for IBS drug trial design.*

*Defining a monthly responder as a subject with at least two of four weeks of response in that month, and an overall responder defined as a monthly responder for at least 2 of the 3 months of the trial, the results do not meet statistical significance for RFIB3008 for the primary endpoints of global IBS symptoms. The treatment difference was 5.3% (p=0.1626) (*Table 11 *on page 43).*

*When the data were analyzed by week and using an overall responder redefined as a subject in response for at least 50% of the weeks of the trial (as per the present FDA Guidance) results are significant for only four of the 12 weeks of the trial. The over-all treatment difference was 4.6%, p=0.2103. The results of the weekly responder analysis indicate that the observed efficacy lasts only for the first 4 weeks after treatment, then decreases after week five. (*Table 12 *on page 43).*

Table 10: Number of Months of Adequate Relief of Global IBS Symptoms Based on Weekly SGA Assessments (ITT Population) – RFIB3008

	Rifaximin 550 mg TID N = 315 n (%)	Placebo N = 320 n (%)
Number of Months Subject had Adequate Relief of Global IBS Symptoms		
During Month 1		
0	168 (53)	202 (63)
1	147 (47)	118 (37)
	Odds ratio = 1.50 95% CI = 1.09 to 2.06 p = 0.0121	
During Month 1 plus Month 2		
0	145 (46)	180 (56)
1	68 (22)	58 (18)
2	102 (32)	82 (26)
	Odds ratio = 1.48 95% CI = 1.10 to 1.99 p = 0.0103	
During Months 1, 2, and 3		
0	139 (44)	177 (55)
1	59 (19)	41 (13)
2	32 (10)	41 (13)
3	85 (27)	61 (19)
	Odds ratio = 1.52 95% CI = 1.13 to 2.03 p = 0.0053	

Source: Summary Table 14.2.5a (Section 14.2); corresponding Data Listings 16.2.6.1 and 16.2.6.4 (Appendix 16.2.6).
Abbreviation: CI = confidence interval.
Notes: A subject achieved adequate relief if he/she answered "Yes" to the weekly SGA question for ≥ 2 weeks per month. Subjects who received antibiotics or > 2 doses of prohibited medications were entered as nonresponders from time of beginning the medications, regardless of the actual response data.
The p-value and odds ratio were obtained using the proportional odds model for ordinal outcome with fixed effects for treatment arm and analysis center.

Table 11: Monthly Responder Rate of Adequate Relief of IBS Symptoms by Treatment Group (LOCF, ITT))

Study 3008				
	PLA	**RFX**	**Diff (RFX-PLA)**	**Chi-square p-value**
Month 1	118/320 (36.9%)	147/315 (46.7%)	9.8%	0.0124
Month 2	104/320 (32.5%)	125/315 (39.7%)	7.2%	0.0595
Month 3	84/320 (26.3%)	106/315 (33.7%)	7.4%	0.0417

Table 12: Weekly Responder Rate of Adequate Relief of IBS Symptoms by Treatment Group

Study 3008				
	PLA	**RFX**	**Diff (RFX-PLA)**	**Chi-square p-value**
Week 1	85/314 (27.1%)	98/312 (31.4%)	4.3%	0.2326
Week 2	121/315 (38.4%)	129/311 (41.5%)	3.1%	0.4335
Week 3	96/312 (30.8%0	127/310 (41.0%)	10.2%	0.0080
Week 4	94/310 (30.3%)	119/308 (38.6%)	8.3%	0.0297
Week 5	87/308 (28.3%)	110/308 (35.7%)	7.4%	0.0469
Week 6	102/307 (33.2%)	99/308 (32.1%)	-1.1%	0.7749
Week 7	93/307 (30.3%)	108/308 (35.1%)	4.8%	0.2072
Week 8	91/307 (29.6%)	105/308 (34.1%)	4.5%	0.2364
Week 9	84/307 (27.4%)	97/308 (31.5%)	4.1%	0.2609
Week 10	85/307 (27.7%)	100/308 (32.5%)	4.8%	0.1962
Week 11	76/307 (24.8%)	87/308 (28.3%)	3.5%	0.3267
Week 12	72/307 (23.5%)	94/308 (30.5%)	7.0%	0.0484

10 Additional Efficacy Evaluations

10.1 FDA-Requested Endpoint – Abdominal Pain and Stool Consistency Responders

Medical Officer's Comments:
In response to a request from the Division, the proportions of subjects who were responders for the abdominal pain and stool consistency endpoint (abdominal pain and stool consistency) as defined by the FDA Guidance for IBS, and each component endpoint were analyzed as exploratory analyses

Analyses of the FDA-requested endpoints do demonstrate efficacy during the Primary Efficacy Period of week 3 thru 6. There was an approximate 10% treatment difference observed between groups during the PEP; however, efficacy beyond the PEP time frame was not demonstrated in both trials - in both the FDA weekly and monthly analysis.

10.2 Subpopulations

Medical Officer's Comments:
The subpopulation analysis showed consistency across groups for both trials, except for non-white subjects (<10%). However, the sample size of this subgroup was too small to draw statistically or clinically meaningful conclusions.

11 Review of Safety

Safety Summary

The safety of rifaximin in this population appears acceptable. The drug is poorly absorbed and there is little systemic exposure in the original or metabolized form. The most common side effects seen were headache (rifaximin 5.3% vs. placebo 6.2%), nausea (4.4% vs. 3.7%), diarrhea (3.4% vs. 3.1%) and urinary tract infection (3.4% vs. 2.2%). Serious adverse events were reported in 1.5% of rifaximin arm subjects and 2.2% of placebo arm subjects. There were no deaths and no episodes of serious constipation or ischemic colitis.

Reviewer's Comments:

*The safety of rifaximin has been studied in the traveler's diarrhea indication and with long term use (>1 year) with the hepatic encephalopathy indication. In general rifaximin has been found to be safe. Its poor solubility, poor absorption and low systemic exposure makes both its effects and its adverse events mostly confined to the GI tract. Nausea, vomiting and diarrhea are all known adverse events. They occur at a relatively low incidence (*Table 13 *and* Table 14*). There are rare reported events of anaphylaxis, which is listed in the current product labeling.*

The systemic exposure in the IBS population is twice that of the 'normal healthy' population, but is still very low - in the range of nanograms.

Table 13: Overall Summary of TEAE Incidence (Primary Safety Population)

	Rifaximin						
Category	275 mg BID 2 Weeks N = 95 n (%)	550 mg BID 2 Weeks N = 190 n (%)	550 mg BID 4 Weeks N = 96 n (%)	550 mg TID 2 Weeks N = 624 n (%)	1100 mg BID 2 Weeks N = 98 n (%)	All Rifaximin N = 1103 n (%)	Placebo N = 829 n (%)
Any TEAEs	50 (52.6)	95 (50.0)	42 (43.8)	340 (54.5)	52 (53.1)	579 (52.5)	436 (52.6)
TEAEs by Intensity							
Severe	5 (5.3)	14 (7.4)	3 (3.1)	36 (5.8)	5 (5.1)	63 (5.7)	53 (6.4)
Moderate	21 (22.1)	35 (18.4)	15 (15.6)	161 (25.8)	14 (14.3)	246 (22.3)	214 (25.8)
Mild	24 (25.3)	46 (24.2)	24 (25.0)	142 (22.8)	32 (32.7)	268 (24.3)	169 (20.4)
Not applicable	0	0	0	1 (0.2)	1 (1.0)	2 (0.2)	0
TEAE Related to Study Drug	10 (10.5)	25 (13.2)	9 (9.4)	75 (12.0)	15 (15.3)	134 (12.1)	89 (10.7)
Serious TEAEs	1 (1.1)	2 (1.1)	0	10 (1.6)	3 (3.1)	16 (1.5)	18 (2.2)
TEAEs Resulting in Study Discontinuation	3 (3.2)	7 (3.7)	2 (2.1)	8 (1.3)	2 (2.0)	22 (2.0)	14 (1.7)
All Deaths	0	0	0	0	0	0	0

Source: ISS Table 5.1 (IBS), Appendix C
Abbreviations: BID = twice daily; IBS = irritable bowel syndrome; TEAE = treatment-emergent adverse event; TID = 3 times daily
Note: A TEAE is defined as an adverse event that started on or after first dose date.

Table 14: Treatment Phase TEAEs occurring in at Least 2% of All Rifaximin or Placebo treated Subjects (Primary Safety Population)

	Rifaximin						
System Organ Class Preferred Term	275 mg BID 2 Weeks N = 95 n (%)	550 mg BID 2 Weeks N = 190 n (%)	550 mg BID 4 Weeks N = 96 n (%)	550 mg TID 2 Weeks N = 624 n (%)	1100 mg BID 2 Weeks N = 98 n (%)	All Rifaximin N = 1103 n (%)	Placebo N = 829 n (%)
Any TEAEs	45 (47.4)	76 (40.0)	35 (36.5)	178 (28.5)	46 (46.9)	380 (34.5)	273 (32.9)
Gastrointestinal disorders							
Nausea	5 (5.3)	6 (3.2)	3 (3.1)	16 (2.6)	4 (4.1)	34 (3.1)	19 (2.3)
Abdominal pain	1 (1.1)	3 (1.6)	1 (1.0)	17 (2.7)	4 (4.1)	26 (2.4)	21 (2.5)
Infections and infestations							
Upper respiratory tract infection	4 (4.2)	4 (2.1)	0	4 (0.6)	2 (2.0)	14 (1.3)	19 (2.3)
Nasopharyngitis	0	2 (1.1)	0	4 (0.6)	2 (2.0)	8 (0.7)	20 (2.4)
Nervous system disorders							
Headache	4 (4.2)	5 (2.6)	5 (5.2)	25 (4.0)	3 (3.1)	42 (3.8)	36 (4.3)

Source: ISS Table 5.2.2.1 (IBS), Appendix C
Abbreviations: BID = twice daily; IBS = irritable bowel syndrome; TEAE = treatment-emergent adverse event; TID = 3 times daily

12 References

[1] Brandt, L, et al: American College of Gastroenterology Task Force on Irritable Bowel Syndrome; Volume 104 supplement 1 January 2009
[2] Spiegel, BMR, Questioning the Bacterial Overgrowth Hypothesis of Irritable Bowel Syndrome: An Epidemiologic and Evolutionary Perspective. Clinical Gastroenterology and Hepatology
[3] Editorial. Rifaximin for Diarrhea-Predominant IBS-Not so fast my friend. Clin Gastroenterol Hepatol 2011;9:281-283.
[4] Khazeni, N, Letter to the Editor; Rifaximin for Irritable Bowel Syndrome without Constipation, NEJM April 14, 2011; 1647-8.
[5] Collins BS and Lin HC. Double-Blind Placebo-controlled Antibiotic Treatment Study of Small Intestinal Bowel Bacterial overgrowth in Children with Chronic Abdominal Pain. J Pediatr Gastroenterol Nutr 2011;52:382-386.
[6] Gerding DN and Johnson S. Management of *Clostridium difficile* Infection: Thinking Inside and Outside the Box. Clinical Infectious Diseases 2010; 51(11):1306–1313.
[7] Jaing ZD, DuPont HL, LaRocca L et al ; In vitro susceptibility of *Clostridium difficile* to rifaximin and rifampin in 359 consecutive isolates at a university hospital in Houston, Texas. I. *J Clin Pathol* 2010;63:355-358.
[8] Derek Yu, Frank Cheeseman, Stephen J. Vanner; Detection of Small Intestinal Bacterial Overgrowth in Irritable Bowel Syndrome: Comparison of Lactulose Hydrogen Breath Test with Scintigraphic Oro-Cecal Transit Study; AGA abstracts
[9] Eric D. Shah, Robert J. Basseri , Kelly Chong , Mark Pimentel; Abnormal Breath Testing in IBS: A Meta-Analysis; Dig Dis Sci (2010) 55:2441–2449
[10] Yu D, Cheeseman F, Vanner S.; *COMBINED OROCECAL SCINTIGRAPHY AND LACTULOSE HYDROGEN BREATH TESTING DEMONSTRATE THAT BREATH TESTING DETECTS OROCECAL TRANSIT, NOT SMALL INTESTINAL BACTERIAL OVERGROWTH IN PATIENTS WITH IRRITABLE BOWEL SYNDROME; GASTROENTEROLOGY* Vol. 141, No. 3, pg 1118
[11] Maxion-Bergemann, S et al; Costs of Irritable Bowel Syndrome in the UK and US, Pharmacoeconomics 2006; 24 (1): 21-37
[12] Scarpellini et al. (2007) High dose rifaximin for the treatment of small intestinal bacterial overgrowth. Aliment Pharmacol Ther;25:781–786
[13] Lauritano C Gabrielli M, Lupascu A, et al. Rifaminin dose-finding study for the treatment of small intestinal bacterial overgrowth. Aliment Pharmacol Ther. 2005a Jul 1; 22(1): 31-5
[14] Pimental M, Park S, Mirocha J, et al. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. Ann Intern Med 2006 October;145(8):557-63